Renal Disease/Nephropathy

- ❖ Screen urine for evidence of renal disease every year in both type 1 and type 2 diabetes.
- ❖ For patients with nephropathy, the major goal is to maintain BP < 130/80 mmHg.
- ❖ Achieving target glucose goals reduces the risk and/or slows the progression of nephropathy.

When should screening occur for diabetic renal disease?

The first clinical evidence of diabetic nephropathy is the appearance of a small excess amount of albumin in the urine termed *microalbuminuria* (> 30 mg albumin excretion per day). Persons with microalbuminuria are referred to as having *incipient nephropathy* and are likely to progress to clinical proteinuria and decreasing renal function over a period of years.

Clinical proteinuria is defined as > 150 mg of protein excretion per day. Normally, small amounts of protein can be found in the urine, but usually this does not exceed 150 mg/24 hours, of which about 10 mg is albumin. When the level of albumin in the urine reaches 30 to 300 mg/day, it is considered low-level albuminuria or microalbuminuria. If the level is greater than 300 mg/day, it is termed macroalbuminuria. Persons with clinical proteinuria are referred to as having overt nephropathy. Once clinical proteinuria occurs, the risk of progression to end-stage renal disease (ESRD) is high in both type 1 and type 2 disease.

Additionally, microalbuminuria is a marker for increased cardiovascular risk, and, if present, is an indication for screening for vascular disease and aggressive intervention to reduce other cardiovascular risk factors, e.g., dyslipidemia, tobacco use, inactivity. In addition, there is some preliminary evidence to suggest that lowering of cholesterol may also reduce the level of proteinuria.

What is the glomerular filtration rate?

The glomerular filtration rate (GFR) is an estimate of the filtering capacity of the kidneys. It is usually expressed as milliliters (mL) per minute (min) and adjusted to a "standard" body size with a surface area of 1.73 meters^2. The normal GFR ranges between 95 to 120 mL/min/1.73m^2 but it varies depending on age, gender, and body size. GFR remains the most accurate index of kidney function, and is a key element of early management of chronic kidney disease. Refer to Table 11 to view the stages of chronic kidney disease.

Commonly Used Formulas (Cockroft-Gault):

Female:

$$GFR[ml/\min] = 0{,}85 \cdot \frac{(140 - age[y]) \cdot bodyweight[kg]}{72 \cdot serum\ creatinine\ [mg/dl]}$$

Male:

$$GFR[ml/\min] = \frac{(140 - age[y]) \cdot bodyweight[kg]}{72 \cdot serum\ creatinine\ [mg/dl]}$$

Web Links for GFR Calculation:

Refer to the dosage calculators at:

- Cockroft-Gault at: http://www.cato.eu/gfr-cockcroft-gault.html
- National Kidney Foundation at: http://www.kidney.org/kidneydisease/ckd/knowGFR.cfm

To determine your patient's glomerular filtration rate, scroll down on the page and click on "calculate your GFR rate."

Table 11: Stages of Chronic Kidney Disease

Stage	Degree of Damage	GFR (mL/min/1.73 m^2)[a]
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	< 15

GFR = glomerular filtration rate.

When should screening begin?

Because renal disease rarely develops in short duration type 1 diabetes, screening in persons with type 1 diabetes should start with the beginning of puberty or after five years from the initial diagnosis. Because of the difficulty in precise dating of the onset of type 2 diabetes, screening should start at the time of diagnosis.

What screening tests should be used?

The initial screening test in all adult patients is a routine urinalysis because some patients will already have clinical proteinuria (>150 mg/day), which is detectable by routine urinalysis. If the routine urinalysis is positive for protein, a quantitative measure of the amount of proteinuria is indicated. Such measures include spot or 24-hour collection for urinary protein/creatinine ratio.

If the urinalysis is negative, a test for the presence of microalbuminuria is indicated. Three screening methods are available:

1. Albumin/creatinine ratio in a single urine sample
2. 24-hour urine collection for albumin and creatinine
3. Timed collection (4 hour or overnight) for albumin and creatinine

First void or morning samples are preferred for the single urine sample technique. If this timing is not possible, all samples for a given individual should be collected at the same time of day to minimize the effect of normal diurnal variation in albumin excretion.

Specific assays are required to detect microalbuminuria as routine urinalysis and other standard assays for protein are not sufficiently sensitive. Screening with reagent tablets or dipsticks specific for microalbuminuria are 95 percent sensitive and 93 percent specific. However, because testing by reagent tablets or dipsticks is subject to error from alterations in urine concentration, all positive results should be confirmed by one of the three more specific methods mentioned

above. Because there is day-to-day variability in albumin excretion, at least two of three collections done in a three to six month period should show elevated levels before designating a patient as having microalbuminuria. Refer to Figure 5 for algorithm of current recommendations for screening for renal disease.

Table 12: Categorization of Abnormalities in Albumin and Protein Excretion

Category	Spot Collection	24-Hour Collection	Timed Collection
Normal	< 30 ug albumin/mg creatinine	< 30 mg albumin/24 hours	< 20 ug albumin/minute
Microalbuminuria	30 to 299 ug albumin/mg creatinine	30 to 150 mg albumin/24 hours	20 to 199 ug albumin/minute
Clinical proteinuria*	> 300 ug protein/mg creatinine*	> 150 mg protein/24 hours	> 200 ug protein/minute

*Some nephrologists suggest that once clinical proteinuria is detected, teasing out that portion of total protein that is albumin adds no useful information.

What are treatment options and goals for patients with diabetic nephropathy?

Facts:

- Achieving normoglycemia will decrease the rate of progression to overt nephropathy.
- Lowering blood pressure will retard the development of overt nephropathy and decrease its rate of progression.
- Angiotension converting enzyme inhibitors (ACEIs) or Angiotensin II receptor blockers (ARBs) should decrease the level of albuminuria/proteinuria and the rate of progression to ESRD.

Options:

- ACE inhibitors or ARB use has been emphasized for nephropathy screening and treatment by the ADA (2008). Ace inhibitors are indicated in all type 1 patients with microalbuminuria even if they are normotensive. Use of ACE inhibitors in normotensive type 2 patients with microalbuminuria is less substantiated by studies. If a type 2 patient has progression in the amount of albuminuria or develops hypertension, ACE inhibitor or ARB treatment then becomes clearly indicated.
- Protein restriction to < 0.8 grams/kg/day is not recommended. Further restriction can be considered in patients with advancing renal dysfunction, symptomatic uremia, or in consultation with a physician experienced in the care of patients with renal disease.
- Tobacco cessation is beneficial for renal function in diabetic patients. There is substantial evidence for the adverse effect of smoking on renal functional deterioration in both type 1 and type 2 diabetes.

Goals:

- The major goal is to maintain BP < 120/80 mmHg.
- Serum creatinine and urinary protein excretion should be measured every three to six months until stable and then annually. (Urinary protein excretion should be measured as an albumin/creatinine ratio in a patient with incipient nephropathy and as a protein/creatinine ratio in a patient with overt nephropathy.)

Goals have not been established for the amount of albuminuria in patients with incipient nephropathy or the amount of proteinuria in patients with overt nephropathy. Expert opinion is that less albuminuria or proteinuria is better. The committee members suggest the following goals:

- For patients with incipient nephropathy (microalbuminuria), the goal of treatment is to stabilize or reduce the urinary albumin/creatinine ratio.
- For patients with overt nephropathy (clinical proteinuria), the goal of treatment is to maintain or reduce the urinary protein/creatinine ratio to < 1.

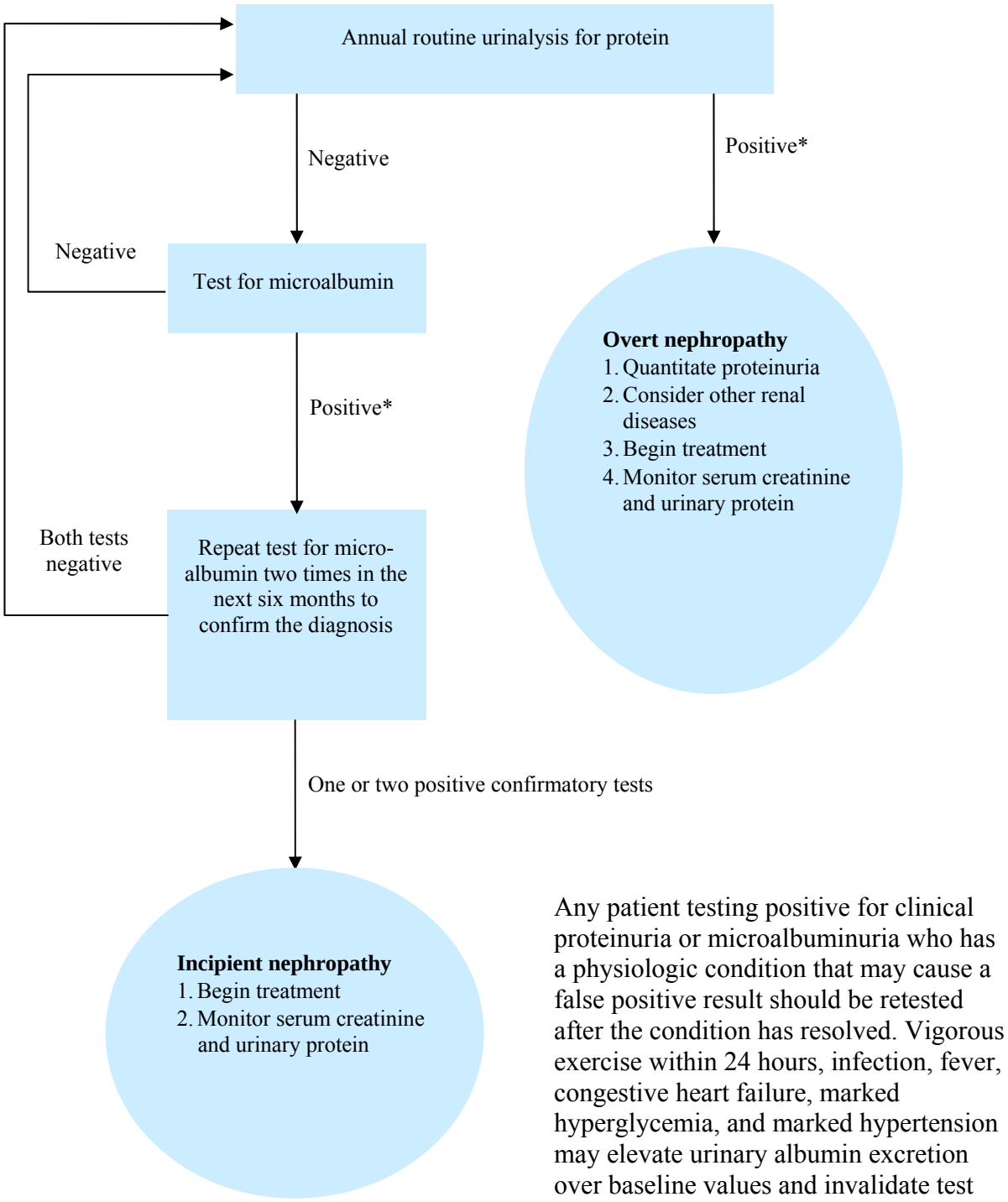
(Currently available therapy does not necessarily ensure that even these goals can be achieved.)

Figure 5 is listed after the reference page.

References:

1. Diabetic Retinopathy, *Diabetes Care,* Volume 25, Supplement 1, January 2002; pps S90-S93.
2. Aiello, LP et al., Diabetic retinopathy (Technical Review). *Diabetes Care* 21:143-156, 1998.
3. Bloomgarden, Z. (2001). Angiotensin II receptor blockers and nephropathy trials, *Diabetes Care*, *24*, 1834-1838.
4. American Diabetes Association. (2007). Standards of medical care in diabetes. *Diabetes Care, 30*(Supplement 1), S4-S41.
5. Gilbert, R., Connelly, K., Kelly, D., Pollock, C., & Krum, H. (2005). Heart failure and nephropathy: Catastrophic and interrelated complications of diabetes. *Clinical Journal of American Society of Nephrologists, 1,* 193-208.
6. Barratt, J. & Topham, P. (2007). Urine proteomics: The present and future of measuring urinary protein components in disease. *Canadian Medical Association Journal, 177*(4), 361-368.
7. Manjunath, G., Sarnak, M., & Levey, A. (2001). Estimating the glomerular filtration rate: Do's and don'ts for assessing kidney function. *Postgraduate Medicine, 110*(6), 55-62.
8. American Diabetes Association. (2008). Standards of medical care in diabetes-2008. *Diabetes Care, 31*(Supplement 1), S12-S54.
9. Cato Computer Therapy for Oncology. (2007). Dosage calculator for GFR by Cockcroft-Gault. Available online at: http://www.cato.eu/gfr-cockcroft-gault.html.
10. National Kidney Foundation. (2008). Glomerular filtration rate (GFR). Available online at: http://www.kidney.org/kidneydisease/ckd/knowGFR.cfm.
11. Rigalleau, V., Lasseur, C., Perlemoine, C., Barthe, N., Raffaitin, C., Liu, C., Chauveau, P., Baillet-Blanco, L., Beauvieux, M.C., Combe, C., & Gin, H. (2005). Estimation of glomerular filtration rate in diabetic subjects. *Diabetes Care, 28*, 838-843.

Figure 5: Screening for Renal Disease



Any patient testing positive for clinical proteinuria or microalbuminuria who has a physiologic condition that may cause a false positive result should be retested after the condition has resolved. Vigorous exercise within 24 hours, infection, fever, congestive heart failure, marked hyperglycemia, and marked hypertension may elevate urinary albumin excretion over baseline values and invalidate test results.